

**American Dental Association's Comments on FDA's Proposed Rule and
Special Control Guidance on Dental Amalgam Products**
[Docket No. 01N-0067]

The American Dental Association ("ADA") submits these comments in support of the Food and Drug Administration's ("FDA" or "the Agency") proposed rule on dental amalgam products and draft guidance document entitled "Special Control Guidance Document on Encapsulated Amalgam, Amalgam Alloy, and Dental Mercury Labeling; Draft Guidance for Industry and FDA" (hereinafter "Draft Guidance"). The ADA is a not-for-profit organization representing its member dentists who number approximately 141,000.

The proposed rule and notice of availability of the Draft Guidance were published in the Federal Register on February 20, 2002 (67 *Fed. Reg.* 34 (2002)).

ADA agrees with and supports FDA's proposal to:

- Issue a separate classification regulation for encapsulated amalgam alloy and dental mercury (hereinafter "encapsulated amalgams"), a preamendments device intended to be mixed in a single-use capsule to form filling material for the treatment of dental caries, as a class II device with special controls;
- Amend the existing classification for amalgam alloy, a class II preamendments device, by adding special controls; and
- Reclassify from class I (general controls) to class II with special controls dental mercury, a preamendments device intended for use as a component of amalgam alloy in the restoration of a dental cavity or broken tooth.

ADA takes the position that, pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") § 513 (a)(1)(B), the FDA is justified in implementing these proposed modifications to its regulations and that there is sufficient information to establish that the special controls described in: (1) the Draft Guidance; (2) the International Standards Organization's "(ISO) 1559:1995 Dental Materials – Alloys for Dental Amalgam" (hereinafter the "ISO Specifications"); and (3) the American National Standards Institute/American Dental Association's "Specification No. 6-1987 for Dental Mercury" (hereinafter the "ANSI/ADA Specifications") will provide a reasonable assurance of the safety and effectiveness of these three categories of devices.

The following comments first provide an overview as to the specific regulatory classification scheme the Agency is proposing with regard to dental amalgam products. The comments then address the scientific evidence that FDA has reviewed in accordance with a comprehensive methodological process to justify this regulatory action. Next, the comments discuss why, from a regulatory perspective, a uniform class II classification with special controls is the appropriate regulatory categorization for the dental amalgam products. The comments then describe why a hearing on this proposed rule is unnecessary. Next, the comments provide summaries of additional scientific evidence provided by ADA in support of the proposed rule. Finally, the comments address why the proposed rule should preempt conflicting state laws regarding dental amalgam products.

I. Overview

In light of the Agency's extensive scientific review related to dental mercury and amalgams outlined more fully below, the FDA has reconsidered its regulatory approach to dental amalgam products and is proposing to regulate these devices in a uniform manner as class II devices with special controls. The Agency may classify a device as class II with special controls if it determines that general controls alone will not provide the necessary reasonable assurance of safety and effectiveness. FDC Act § 513 (a)(1)(B). ADA fully supports the Agency's proposed classification scheme of dental amalgam products, which includes a separate classification regulation for encapsulated amalgams as well as the application of class II special controls to all three dental amalgam products that clearly provide a reasonable assurance of safety and effectiveness. As explained below, the concerns that have been raised in the scientific literature regarding the safe use of dental amalgam products are fully addressed by the Agency's proposed special controls.

Encapsulated Amalgams. Currently, encapsulated amalgams are not regulated as a separate medical device. Rather, they are regulated as class II devices under the amalgam alloy classification. FDA proposes to create a separate class II classification regulation for encapsulated amalgams with special controls. The proposed special controls would consist of conformance to voluntary industry standards described in the ISO Specifications, the ANSI/ADA Specifications, and FDA's Draft Guidance.

Dental Mercury. Dental Mercury is currently regulated as a class I device. FDA is proposing to reclassify dental mercury as a class II device with special controls. The proposed special controls would consist of conformance to voluntary industry standards described in the ANSI/ADA Specifications and FDA's Draft Guidance.

Amalgam Alloy. Amalgam alloy is currently regulated as a class II device. Currently, no performance standard or other special controls have been adopted for amalgam alloy. FDA proposes to amend the class II classification regulation of amalgam alloy to provide for special controls. The proposed special controls would consist of conformance to voluntary industry standards described in the ISO Specifications and FDA's Draft Guidance.

The proposed rule encompassing all three dental amalgam devices is clearly a more rigorous regulatory scheme than that which currently exists. ADA wholly agrees that encapsulated amalgams, amalgam alloy, and dental mercury should be uniformly classified as class II devices, and that the proposed special controls adequately address the risks associated with these devices. FDA and ADA, along with numerous other organizations described below, have conducted extensive studies of the potential risks and adverse health effects associated with dental amalgam products. ADA agrees with the Agency's determination that, upon review of the scientific evidence, there are no major health risks associated with the use of encapsulated amalgams, amalgam alloy, and dental mercury. ADA also agrees that the proposed special controls will adequately address the risks associated with

improper handling of dental amalgam products and the risks to the small subpopulation of individuals who are allergic to the ingredients of these products.

II. The FDA Process Supporting the Proposed Rule

A. The Agency's Scientific Review Related to Dental Amalgam Products Has Been Complete and Appropriate

The proposed rule and Draft Guidance at issue are the result of many years of study and evaluation of the safety of dental amalgam products. The Agency has carefully examined extensive information about the safety of dental restorative materials that contain mercury. Public concern about the safety of dental amalgam engendered several national and international comprehensive reviews of scientific information about the risks and benefits of these products. FDA has carefully studied the reports prepared by the Public Health Service on the topic, as well as information submitted in support of citizen petitions and numerous reports by international health organizations. FDA undertook this review in an effort to promulgate the appropriate classification regulation for these three categories of devices. ADA agrees that the results of this scientific literature review support the uniform classification of these dental amalgam products as class II devices with special controls.

From 1991 to 1992, the U.S. Public Health Service ("PHS") performed a comprehensive risk assessment of dental amalgam. In 1993, the PHS issued a

report on its findings ("1993 PHS Report") 1/ and concluded that historic experience with dental amalgams did not offer persuasive evidence of adverse health effects related to amalgam treatments other than a few reported cases of hypersensitivity. Specifically, a Risk Assessment Subcommittee of the PHS, comprised of 34 senior level experts from the fields of health promotion and disease prevention, dentistry, dental materials, toxicology, and biostatistics, reviewed nearly 120 publications that reported the results of studies on levels of exposure to mercury and its salts. The Risk Assessment Subcommittee found that available data were not sufficient to indicate that health hazards could be identified in non-occupationally exposed persons.

A companion PHS subcommittee, the Benefits Assessment Subcommittee, reviewed the benefits of dental amalgam products. It concluded that dental amalgam, which had been used successfully to treat millions of individuals for over 100 years, was an effective restorative material. The subcommittee also stated that dental amalgam products had reasonable clinical serviceability, wide potential applications, ease of manipulation, and relatively low cost.

The conclusions reached in the 1993 PHS Report were reaffirmed by

1/ "Dental Amalgam: A Scientific Review and Recommended Public Health Service Strategy for Research, Education, and Regulation," Public Health Service, U.S. Department of Health and Human Services, January 1993.

the PHS in 1995 2/ and 1997 3/. The 1997 PHS Report included information from two PHS-sponsored workshops on mercury and amalgam safety. Both workshops concluded that there was insufficient scientific evidence to link mercury vapor exposure, at typical levels associated with dental amalgam restorations, with an unacceptable health risk to the general population.

Moreover, in response to several citizen petitions filed in 1993 4/ requesting that FDA take various actions regarding dental amalgam and mercury – including banning dental mercury – the Agency convened a group of experts to assess the extensive scientific publications submitted by the petitioners seeking to demonstrate that dental mercury and amalgam were unsafe. The publications cited by the petitioners were grouped by study type (i.e. general toxicology, neurotoxicology, immunotoxicology, epidemiology, dental/clinical materials) and disseminated to scientific specialists and dental professionals recruited from various PHS agencies. The government reviewers focused on five major areas of concern: (1) adequate controls; (2) methodological flaws; (3) mercury exposure measurements; (4) relevance of the article to dental amalgam safety assessment; and (5) fetal mercury exposure.

2/ "Update Statement by the U.S. Public Health Service on the Safety of Dental Amalgam," September 1, 1995.

3/ "State of the Science on the Safety of Amalgam and other Restorative Materials," Public Health Service, U.S. Department of Health and Human Services, 1997.

4/ Citizen Petition Docket No. 93P-0424, Citizen Petition Docket No. 94P-0354/CP1, and Citizen Petition from Dr. Baylin et al.

Ultimately, none of the experts who reviewed the petitioners' data concluded that dental amalgam restorations caused adverse health effects to patients. The experts' analyses, like the 1993, 1995, and 1997 PHS Reports, acknowledged that mercury is a well-known toxicant, that its toxicity is dependent on dose, that mercury from amalgam fillings can accumulate in tissues, and that mercury is an allergen sensitizer in some humans. However, significantly, the experts' analyses concluded that there is no evidence in the scientific literature to suggest that individuals with dental amalgam restorations will experience adverse health effects.

Furthermore, The National Institute of Dental and Craniofacial Research initiated a two-pronged study 5/ to examine: (1) the establishment of mercury levels from amalgam fillings and the occurrence of various reported health symptoms; and (2) a longitudinal cohort assessment in which the number of amalgam restorations were analyzed retrospectively and comparisons made of reported health effects between groups with high and low exposure levels and those with no exposure. To date, no discernable causal or correlational connection has been observed between study subjects with amalgam fillings and adverse health effects.

In addition, FDA has evaluated a number of reports from international authorities that both assessed the available body of scientific literature as well as

5/ "Casa Pia Study of Dental Amalgams in Children; Children's Amalgam Trial," National Institute of Dental and Craniofacial Research.

reviewed the opinions of leading researchers and renowned experts in the fields of oral health, toxicology, medicine, and other related disciplines. Expert groups from Sweden 6/, New Zealand 7/, Canada 8/, and the European Commission all concluded that mercury exposure from dental amalgams does not have an adverse effect on health, with the exception of isolated cases of allergic reactions. Likewise, a report generated from a nine-country information exchange 9/ concluded that no systemic dose-dependent toxic effects have been shown to be related to dental amalgams. Also, several studies included in a comprehensive report published by the World Health Organization 10/ concluded that, while it is well documented that individuals with dental amalgam fillings have higher concentrations of mercury in tissues than those without amalgam fillings, there is no direct evidence of an adverse effect of mercury from amalgam tooth fillings on general health.

6/ "Possible Health Effects and Dental Amalgam," Swedish National Board of Health and Welfare, 1994.

7/ "Dental Amalgam and Human Health (A Current Consensus)," WHO Collaborating Centre in Oral Health, Wellington School of Medicine, University of Otago, Wellington, New Zealand, June 1996.

8/ "The Safety of Dental Amalgam," Health Canada, 1995; "The Safety of Dental Amalgam: A State of the Art Review," Conseil d'Evaluation des Technologies de la Sante de Quebec, April 1997.

9/ Dental Amalgam – A Report with Reference to the Medical Devices Directive 93/42/EEC from and Ad Hoc Working Group Mandated by the European Commission, June 1998.

10/ "Consensus Statement on Dental Amalgam," World Health Organization Consultation on Assessing the Risks and Benefit to Oral Health, Oral Care, and Environment Using Dental Amalgam and its Replacement, and FDI World Dental Federation, 1997. See also "Dental Amalgam and Alternative Direct Restorative Materials," World Health Organization, 1997.

Finally, FDA requested in 1993 that its Dental Products Advisory Panel ("Panel") make a classification recommendation for the encapsulated amalgams product 11/. After reviewing updated literature and hearing testimony from representatives of FDA, ADA, and the PHS, the Panel unanimously recommended to classify encapsulated amalgams into class II with special controls. The panel concluded there were no major health risks associated with encapsulated amalgams when used as directed, but the Panel also recognized that there was a small population of patients that could experience allergic reactions to the materials in amalgam.

It is clear that FDA has not ignored the scientific evidence on this issue, nor has the Agency rushed to judgment in its determination that uniformly classifying the three dental amalgam products as class II devices with special controls will provide a reasonable assurance of the safety and effectiveness of these devices. Indeed, just the opposite is true. The Agency has taken its time to gather and evaluate all relevant studies in order to determine the proper classification regulation of dental amalgam products. The scientific literature supports the Agency's conclusion that the benefits of encapsulated amalgam, amalgam alloy, and dental mercury far outweigh any potential adverse health effects. In fact, as discussed below, the labeling requirements in the special control documents adequately protect the small population of patients who could experience allergic

11/ Transcript from 1993 meeting of the Food and Drug Administration Dental Products Advisory Panel, December 1-3, 1993; Transcript from 1994 meeting of the Food and Drug Administration Dental Products Advisory Panel, June 29, 1994.

reactions from dental amalgams as well as occupationally exposed health care workers.

B. Class II with Special Controls Is the Appropriate Level of Regulation for Dental Amalgam Products

The FDC Act promulgated a classification scheme for the regulation of medical devices intended for human use depending on the regulatory controls needed to provide a reasonable assurance of their safety and effectiveness. Under the Medical Device Amendments of 1976, a device was classified into class II if there was insufficient information to show that general controls alone would assure safety and effectiveness, but there was adequate information to establish performance standards that would provide this assurance. The passage of the Safe Medical Devices Act of 1990 ("SMDA") amended the FDC Act to allow FDA to require special controls for class II devices as well as specific performance standards. FDC Act § 513 (a)(1)(B) currently permits the classification of devices into class II with special controls if the Agency concludes that the special controls provide a reasonable assurance of safety and effectiveness. Pursuant to FDC Act § 513(a)(2)(C), this determination of safety and effectiveness through the use of special controls is made primarily through a balancing of the probable benefits to health from the use of the device with the probable risks of injury or illness from such use.

ADA agrees with the Agency's determination that under FDC Act § 513(a)(2)(C) the probable benefits associated with the use of encapsulated amalgams, amalgam alloy, and dental mercury outweigh the probable risks of using

these products. The potential risks of amalgam are generally applicable only to a small population of patients who may experience allergic reactions to the materials in amalgam, as well as to health care workers who may have occupational exposure due to the mishandling of dental amalgam products. The known benefits of dental amalgam products include a broad range of applicability in clinical situations, reasonable serviceability, durability, ease of use, relatively low cost, and relative insensitivity to variations in handling technique and oral conditions. ADA fully concurs with FDA's conclusion that valid scientific evidence exists to determine the safety and effectiveness of dental amalgam products with the use of special controls. Moreover, the extensive scientific evidence submitted by ADA in these comments also supports the Agency's conclusion that dental amalgam products are safe and effective with the use of special controls.

ADA also agrees that the potential benefits and potential risks of the dental amalgam products are sufficiently characterized such that the appropriate level of regulation for these products is class II with special controls. The potential risks of allergic reactions to dental amalgam products and the risks associated with the mishandling of these three categories of devices are fully addressed in the proposed rule. The ADA agrees that the special controls proposed by the FDA will address those risks presented by dental amalgam products, both to the hypersensitive individuals and health care workers. Reasonable protection against these adverse health effects is precisely what the special controls are intended to achieve. The recommendations set forth in the Draft Guidance, ISO Specifications,

and ANSI/ADA Specifications provide a reasonable assurance that those with allergies to the materials in amalgam will be made aware of the products' contents prior to use. Likewise, the special controls provide health care workers who handle the products with explicit instructions as to proper handling procedures.

1. Draft Guidance

The purpose of a guidance document is to provide assistance to the regulated industry by clarifying requirements that have been issued in regulations by FDA. In the proposed rule on dental amalgam products, the Draft Guidance is proposed as a special control applicable to encapsulated amalgams, amalgam alloy, and dental mercury, and represents the Agency's current thinking on the content and format of labeling of these products. The Draft Guidance describes a means by which manufacturers of the three dental amalgam products addressed in the document may comply with the requirements of class II special controls. ADA supports FDA's proposal of the Draft Guidance as a special control as it provides a reasonable assurance of safety and effectiveness for all three dental amalgam products.

The Draft Guidance clearly addresses the potential risks for those individuals who are allergic to ingredients in the dental amalgam products, as well as the risks related to improper handling of these devices. The Draft Guidance recommends that all encapsulated amalgams, amalgam alloy, and dental mercury products bear conspicuous labels that list all ingredients based upon the descending order of the weight percentage, including all component elements. This information

will enable the clinician to avoid using the product if it contains ingredients to which the patient is known to be allergic. The Draft Guidance also recommends labeling that instructs clinicians not to use the product in hypersensitive persons and includes instructions to follow in the event of an allergic reaction. This guidance also recommends instructions for storage, handling, and use to address the potential toxicity risks related to improper storage, trituration, and handling by health care workers. The Draft Guidance also includes recommendations that manufacturers of these dental amalgam products adhere to additional standards set forth in the ISO Specifications and the ANSI/ADA Specifications.

2. ISO Specifications

The ISO Specifications contain several recommendations that also address the potential risks associated with encapsulated amalgams and amalgam alloy. These specifications were developed by the International Standards Organization in conjunction with international governmental and non-governmental committees. The ISO Specifications focus on the consistency of chemical composition and the important physical properties of the restorative material.

Specifically, the ISO Specifications address the appropriate provisions and test methods for alloys used in amalgam. They set forth the minimum silver content, and the maximum content of tin, copper, indium, palladium, platinum, zinc, and mercury. They also recommend proper physical properties of the alloy, i.e. the maximum percent creep, percent dimensional change, and compressive strength

after one hour and after 24 hours. The ISO Specifications recommend test methods for determining these physical properties. These recommendations serve to inform clinicians about what substances are in the dental amalgam products so that potential allergic reactions can be avoided. They also specify minimum performance characteristics necessary for clinical use. Furthermore, the ISO Specifications address the potential risks to health care workers by providing recommendations, specifications, and instructions as to storage, proper handling, and trituration. Finally, they contain packaging and labeling instructions that are generally consistent with those proposed in the Draft Guidance. ^{12/}

3. ANSI/ADA Specifications

The ANSI/ADA Specifications also contain several recommendations to address the potential risks associated with encapsulated amalgams and dental mercury. These specifications address specific mercury-related issues to inform the dentist of the physical properties of the mercury to be used in restorations. Such awareness will, again, allow the dentist to avoid potential allergic reactions to the dental amalgam products.

The ANSI/ADA Specifications articulate the specifications and test methods for mercury suitable for the preparation of dental amalgam. They also recommend packaging in air-tight containers and providing hazard warnings regarding mercury hygiene. The occupational risks associated with these products,

^{12/} The ISO Specifications do not suggest the listing of an ingredient present in the alloy in concentrations less than 0.1% mass/mass. In contrast, FDA's Draft Guidance recommends the listing of all ingredients.

such as toxicity from improper handling and storage, are covered in the ANSI/ADA Specifications through detailed recommendations for mercury manipulation and its packaging information, transport, and handling procedures.

In sum, ADA supports the class II level of regulation of the dental amalgam products with the special controls addressed above, because such classification provides a reasonable assurance of the safety and effectiveness of these products. The scientific evidence points to two main groups of individuals who could potentially experience adverse health effects from dental amalgam: hypersensitive patients who may experience allergic reactions to the ingredients in amalgam and health care workers occupationally exposed to mercury. The special controls described in the Draft Guidance, ISO Specifications, and ANSI/ADA Specifications provide adequate and reasonable protections against the remote potential risks of the use of these products. Therefore, a uniform class II classification with special controls for encapsulated amalgams, amalgam alloy, and dental mercury is entirely proper.

C. Administrative Hearing on Proposed Rule Not Necessary

The ADA supports FDA's decision not to hold a formal administrative hearing with respect to this proposed rule. An administrative hearing on the proposed classification level of encapsulated amalgams, amalgam alloy, and dental mercury is not required, nor is such a hearing necessary. The regulations governing hearings on proposed rules are codified in 21 C.F.R. § 10.40(f) and state:

In addition to the notice and public procedure required under paragraph (b) of this section, the Commissioner may also subject a

proposed or final regulation, before or after publication in the Federal Register, to the following additional procedures:

- (1) Conferences, meetings, discussions, and correspondence under § 10.65.
- (2) A hearing under Parts 12, 13, 14, or 15.
- (3) A notice published in the Federal Register requesting information and views before the Commissioner determines whether to propose a regulation.

(emphasis added). Part 12 of the Code of Federal Regulations, referenced above, is entitled "Formal Evidentiary Public Hearing," and states as to its scope:

The procedures in this part apply when—

- (a) A person has a right to an opportunity for a hearing under the laws specified in § 10.50; or
- (b) The Commissioner concludes that it is in the public interest to hold a formal evidentiary public hearing on any matter before FDA. 13/

Simply put, FDA *may* hold a formal evidentiary hearing on the proposed rule on dental amalgam products if the Agency concludes that it is in the public interest to do so. There is no specific statutory requirement mandating such a hearing.

There is no "public interest" need to hold an evidentiary hearing on the proposed rule on the dental amalgam products. As described above, in formulating the proposed classifications, the Agency considered several reports on this issue from the U.S. Public Health Service; studies and reports reviewed by international health organizations and foreign governments; other U.S. government sponsored

13/ 21 C.F.R. § 12.1. It is important to note that 21 C.F.R. § 10.50, referenced above, does not apply to the proposed rule on dental amalgam products.

studies; voluminous information submitted in support of citizen petitions requests; recommendations from the Dental Products Advisory Panel; and the significant human experience with amalgam for over 100 years. For years, the Agency has been evaluating the scientific evidence as to the safety of the dental amalgam products, and those opposed to the use of such products have had ample time to submit information in favor of their position both before the publication of the proposed rule and during the notice and comment period. In fact, FDA has reviewed numerous reports and studies calling for the outright ban of dental amalgam products in the United States. A hearing on the proposed rule would be inefficient for no new facts would likely come to bear. In addition, holding a public hearing would only slow down the reclassification of these dental amalgam products, which (as described above) imposes more rigorous regulatory requirements on these products than currently exist.

III. ADA's Scientific Review Related to Dental Mercury and Amalgam

Based on currently available scientific evidence, ADA has concluded that dental amalgam is a safe, affordable and durable material for all but a handful of individuals who are allergic to one of its components. This section first summarizes several of the more recently published studies analyzed by ADA that, together with the exhaustive survey of the scientific literature published by the FDA in the preamble to the proposed rule, confirm the lack of adverse health effects from the use of dental amalgam products. This is followed by ADA's refutation of

the validity of other studies often cited by those opposed to the continued use of amalgam restoration products in dentistry. The ADA believes it is important to address the limitations and misunderstandings surrounding these studies in order to understand why they are not, and should not be, relied on by FDA.

A. Recent Studies that Support the Use of Dental Amalgam Products

Issued in late 1997, the FDI World Dental Federation and the World Health Organization consensus statement on dental amalgam stated, "No controlled studies have been published demonstrating systemic adverse effects from amalgam restorations." The document also concluded that, aside from rare instances of local side effects of allergic reactions, "the small amount of mercury released from amalgam restorations, especially during placement and removal, has not been shown to cause any . . . adverse health effects." 14/

The ADA's Council on Scientific Affairs' 1998 report on its review of recent scientific literature on amalgam similarly states: "The Council concludes that, based on available scientific information, amalgam continues to be a safe and effective restorative material." The Council's report also states, "There currently appears to be no justification for discontinuing the use of dental amalgam." 15/

14/ World Health Organization, FDI World Dental Federation, *supra* note 10 at 9.

15/ "Dental amalgam: update on safety concerns," Journal of the American Dental Association, ADA Council on Scientific Affairs, 1998;129:494-503.

Additionally, there have been several, more recent, peer-reviewed scientific studies concerning the safety of dental amalgam. These studies, abstracted below, refute allegations of a causal link between dental amalgam and various medical conditions:

- Saxe S.R., Wekstein M.W. et al., “Alzheimer’s disease, dental amalgam and mercury,” JADA 1999;130(2):191-99.

This study consisted of 68 human subjects with diagnosed Alzheimer’s disease and 33 control subjects without Alzheimer’s to determine mercury levels in multiple brain regions at autopsy and to ascertain the subjects’ dental amalgam status and history. Conclusions: Mercury in dental amalgam restorations does not appear to be a neurotoxic factor in the pathogenesis of this disease. The authors found that brain mercury levels are not associated with dental amalgam, either from existing amalgam restorations or according to subjects’ dental amalgam restoration history. Furthermore, dental amalgam restorations, regardless of number, occlusal surface area or time, do not relate to brain mercury level.

- Saxe, S.R., Snowdon, D.A. et al., “Dental amalgam and cognitive function in older women: findings from the Nun Study,” JADA 1995;126:495-501.

This article reported on a study that focused on the relationship of dental amalgams with the onset of Alzheimer’s disease. Conclusions: Researchers reported finding “no significant association of Alzheimer’s disease with the number, surface area, or history of having dental amalgam restorations” and “no statistically

significant differences in brain mercury levels between subjects with Alzheimer's disease and control subjects."

- Ahlqwist M., Bengtsson C. et al., "Serum mercury concentration in relation to survival, symptoms, and diseases: Results from the prospective population study of women in Gothenburg, Sweden" Acta Odontol Scand 1999;57(3):168-74.

This prospective population study of women in Gothenburg, Sweden, was started in 1968-69 and comprised 1462 women aged 38-60 years at baseline. Follow-up studies were conducted in 1974-75, 1980-81 and 1992-93. Conclusions: No statistically significant correlation was observed between dental amalgam and the incidence of diabetes, myocardial infarction, stroke or cancer. No association was established between disease and mercury on a population basis in middle-aged and older women.

- Clarkson, T.W., "The Three Faces of Mercury," Environment Health Perspectives 2002;110 (Supp. 1).

This review article describes the perception of risk from the exposure of billions of people to methyl mercury in fish, mercury vapor from amalgam tooth fillings, and ethyl mercury in the form of thimerosal added as an antiseptic to widely used childhood vaccines. Key gaps in current knowledge are identified from the points of view both of risk assessment and of mechanisms of action.

Conclusions: The levels of inorganic mercury in tissue caused by release of vapor from amalgam are well below those associated with overt toxic effects or even with subtler neurobehavioral and renal effects. Furthermore, this review summarizes

the relationship between mercury level in different tissues and Alzheimer's disease and concludes that overall studies in the literature have not produced a convincing picture of any kind of correlation between mercury level and this disease.

- Wahl, M.J., "Amalgam - Resurrection and redemption. Part 1: The clinical mythology of anti-amalgam," Quintessence International 2001; 32(7):525-35.

A literature search revealed that the vast majority of amalgam restorations do not cause fractured cusps or recurrent caries. Most amalgam restorations have been shown to last longer than resin composite restorations. The use of dental amalgam has not been banned in any country in the European Union.

Conclusions: According to the latest scientific information available, dental amalgam is a remarkably durable and long-lasting restorative material. Although its appearance is unaesthetic, its clinical performance and effectiveness are unsurpassed by those of resin composite.

- Dahl JE, Sundby J, et al., "Dental workplace exposure and effect on fertility," Scand J Work Environ Health 1999;25(3):285-90.

This study cohort consisted of 558 female dental surgeons (1/3 of whom placed more than 50 fillings a week) and 450 high school teachers (control) that had given birth in Norway to at least one living child. The study comprised data from a total of 1,408 pregnancies. The effects of practicing dentistry and of the given workplace exposure on fertility were analyzed using the discrete proportional hazard regression method. Conclusions: Occupational exposure to mercury had no clear adverse effects on fertility for the female dental surgeons studied.

- Schuurs AH., "Reproductive toxicity of occupational mercury. A review of the literature," J Dent 1999;27(4):249-56.

This paper analyzed the potential reproductive effects of handling dental silver amalgam. Experimental studies on animals, case reports, and epidemiological studies were reviewed. Conclusions: Negative reproductive effects from exposure to mercury in the dental office are unproven. Consequently, given the low amount of mercury derived from dental amalgam fillings, the population at large is at even less risk of mercury exposure than dental office staff.

- Wahl, M.J., "Amalgam - Resurrection and redemption. Part 2: The medical mythology of anti-amalgam," Quintessence International 2001; 32(3):696-710.

A review of the literature indicated that amalgam restorations release small quantities of mercury but apparently not enough to cause systemic health problems. Mercury from dental amalgam restorations cannot be linked to kidney damage, Alzheimer's disease, multiple sclerosis, other central nervous system diseases including "amalgam disease," mental disorders, damage to the immune system, increases in antibiotic resistance, or harmful reproductive effects.

Conclusions: This review of the latest literature concluded that dental amalgam remains a safe and effective restorative material.

The National Institute of Dental and Craniofacial Research is currently supporting two large clinical trials on the health effects of dental amalgam. Studies under way for several years in Portugal and the northeastern United States involve not only direct neurophysiological measures but also

behavioral and cognitive functional assessments. In addition, the trials are monitoring the impact of amalgam on immune function, antibiotic resistance, and renal function. Conclusions: Preliminary findings from these studies show a lack of a causal relationship between dental amalgams and adverse health effects and are consistent with any number of small and large epidemiological studies published over the years concerning the health effects of dental amalgam.

B. ADA's Refutation of Scientific Evidence that Dental Amalgam Products Are Unsafe

There does exist certain scientific literature that is frequently cited by those who call into question the safety of dental amalgam products. The FDA has already comprehensively addressed the body of available scientific literature often cited by the opponents of amalgam, and the Agency has concluded that there are no major health risks associated with the use of dental amalgam products. Below is ADA's refutation of several of the most frequently cited articles of this nature and others published more recently.

1. Release of Mercury Vapor from Dental Amalgam

Vimy and Lorscheider were the first to perform systematic intra-oral mercury vapor measurements in the mid-1980s to estimate the daily intake of mercury from amalgam fillings. Two of their major publications remain controversial even today.

- Vimy MJ, Lorscheider FL, "Intra-oral air mercury released from dental amalgam," J Dent Res 1985;64:1069-1071.

- Vimy MJ, Lorscheider FL, "Serial measurements of intra-oral air mercury: estimation of daily dose from dental amalgam." J Dent Res 1985;64:1072-1075.

Conclusions: Vimy and Lorscheider estimated that the daily exposure to mercury from dental amalgam is 48 ug, which approaches the limit established by OSHA for inhalation of mercury vapor in a working environment.

ADA Response: Olsson and Bergman have evaluated this study using a comprehensive inspiratory-expiratory air-volume analysis, and concluded that the mercury release was 16 times less than that claimed by Vimy and Lorscheider. Olsson S., Bergman M.J., "Factors affecting estimation of dental amalgam mercury exposure from measurements of mercury vapor levels in intra-oral and expired air." J Dent Res 1987;66:1775-1780. Other investigators have since confirmed this discrepancy (Berglund A., "Estimation by a 24-hour study of the daily dose of intra-oral mercury vapor inhaled after release from dental amalgam," J Dent Res 1990; 69:1646-51; Bjorman L., Lind B., "Factors influencing mercury evaporation rate from dental amalgam fillings," Scand J. Dent Res 1992 Dec;100(6):354-60; Skare L., Engqvist A., "Human exposure to mercury and silver released from dental amalgam restorations," Arch Environ Health 1994;49(5):384-94; Mackert J.R., Jr., Berglund A., "Mercury exposure from dental amalgam fillings: absorbed dose and the potential for adverse health effects," Crit Rev Oral Biol Med 1997;8(4):410-36). The major error committed by Vimy and Lorscheider is their methodology. The use of intra-oral mercury vapor measurements to estimate daily uptake must take into account the differences between the collection volume and flow rate of the

measuring instrument, and the inspiratory volume and the flow rate of air through the mouth during inhalation of a single breath. Their failure to account for these differences resulted in a substantial overestimation of the absorbed dose.

- “Toxicological Profile for Mercury,” Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, 1999.

This updated mercury profile (“1999 ATSDR Report”), which broadly addresses the effects of mercury from all sources, has been cited in various documents by opponents of dental amalgam as support for the alleged adverse health effects associated with these products. Conclusions: The opponents to amalgam claim the 1999 ATSDR Report concludes that mercury vapors released from amalgam pose a major health risk for the developing brains of children.

ADA Response: The opponents selectively cite those studies that were reviewed in the 1999 ATSDR Report that supposedly support their position and ignore those that do not. The fact that a study is included in a literature review does not mean that the reviewers agree with the study’s conclusions. The broad scope of the 1999 ATSDR Report includes a subsection entitled “More on Health Effects and Dental Amalgam” to specifically address the state of the science with regard to dental amalgam. This section states that “[a] number of government sponsored scientific reviews of the literature on the health effects associated with the use of dental amalgam have concluded that the data do not demonstrate a health hazard for the large majority of individuals exposed to mercury vapor at levels commonly encountered from dental amalgam.” 1999 ATSDR Report at 293.

The 1999 ATSDR Report then mentions that certain European countries have placed restrictions on the use of amalgam for environmental reasons, stating “[t]he restrictive actions, however are prospective, and none of the government reports recommend removing existing fillings in people who have no indication of adverse effects attributable to mercury exposure.” Id. This 1999 ATSDR Report does not conclude that dental amalgams pose a major health risk for the developing brains of children. Rather, the report states that “[t]o prevent misleading or unduly alarming the public, the layperson should be informed that the presence of metallic mercury in dental amalgams is, in itself, not sufficient to produce an adverse health effect.” Id. at 294.

2. Biotransformation of Inorganic Mercury into Toxic Organic Mercury

- J. Leisteuvo, T. Leisteuvo, H. Helenius, L. Pyy, M. Osterblad, P. Huovinen and J. Tenovuo, “Dental amalgam fillings and the amount of organic mercury in human saliva,” *Caries Research* 2001;35:163-166.

In this study, investigators took paraffin-stimulated saliva from 187 human subjects and measured both the organic as well as inorganic mercury with a cold-vapor atomic absorption spectrometry. They divided the subjects into amalgam (A), no lifetime exposure to amalgam (NA), and amalgams removed (NAR) groups. The percentages of the study subjects, whose fish eating frequency was <1 per week, were 2.3, 4.7 and 7.1%, respectively. Conclusions: The amount of organic and inorganic mercury concentrations in saliva were significantly higher in subjects with amalgams than in NA and NAR individuals. Therefore, the authors concluded

that amalgam fillings may be a continuous source of organic mercury, and because organic mercury is known to be more toxic than inorganic mercury, inorganic mercury derived from dental amalgam was biotransformed into organic mercury in vivo.

ADA Response: First, there is a major discrepancy in the age of the subjects included in this study:

Group A: mean age 48; range 15-83

Group NA: mean age 24; range 18-65

Group NAR: mean age 50; range 18-65

Amalgams placed 40-50 years ago are not the same as those placed more recently.

The number of amalgam fillings in Group A is large, and the mean number of amalgam surfaces is 22; range 2-51. Second, saliva sampling time varied. Diurnal variation and diet may influence the composition of saliva. Third, study methodology details were sketchy and the authors left many questions unanswered. The authors did not explain the “zero” values in the Hg range, and the investigators used stimulated whole saliva, which is a mixture of secretion from three pairs of different glands; all of them are richly perfused by blood. The authors provide little information on the method and its reliability or reproducibility, e.g., standard curve, percentage of recovery, etc. These deficiencies cast significant doubt as to the conclusions reached by Leistevuo et al.

3. Central Nervous System

- Bittner AC, Jr., Echeverria D, Woods JS, Aposhian HV, Naleway C, Martin MD, Mahurin RK, Heyer NJ, Cianciola M., "Behavioral effects of low-level exposure to mercury among dental professionals: cross-study evaluation of psychomotor effects," Neurotoxicol Teratol. 1998;20(4):429-39.

In this study, a cross-study design was used to evaluate the sensitivities of five psychomotor tasks previously used to assess preclinical (subclinical) effects of low-level mercury (urinary ≥ 55 ug/L). This study pooled dental professional subject populations from six studies (including the one previously reported in 1995) over the preceding six years. The five psychomotor tests were: (1) Intentional Hand Steadiness Test (IHST); (2) finger tapping; (3) the one-hole test; (4) NES Simple Reaction Time (SRT); and (5) hand tremor. Multivariate analyses were conducted following the hierarchical analysis of multiple response (HAMR) approach. Conclusions: The Intentional Hand Steadiness Test (IHST) factor summary score is very highly related ($B = 0.42$, $p > .001$) to the long-transformed urinary mercury at low levels (> 55 ug/L) and holds occupational relevance for dental professionals.

ADA Response: The subjects involved in this study were highly selective (urinary mercury greater than 55 ug/L), and the study subjects' past history of mercury exposure was unknown to the investigators. Peak exposure in the past may play an important role in the neuropsychological deficits observed in these subjects. Albers et al. (Albers JW, Kallenbach LR et al., "Neurological abnormalities associated with remote occupational elemental mercury exposure,"

Ann Neurol 24:651-659) in 1988 demonstrated that the number of peak exposure events may be actually responsible for the neurological damage that is revealed by neurobehavioral tests (i.e., the number of peak exposure events have been shown to be a better predictor of neurological effects associated with exposure to mercury than mean or cumulative Hg exposure levels).

The data presented in this paper may not be applicable to patients with amalgams. In a recent study reported by a group of investigators at the School of Public Health, Columbia University (Factor-Litvak PR, Hasseloren G, Jacobs DM et al. "Mercury-containing amalgam and neuropsychological function in health adults." Journal of Dent Res 80; special issue (absts. 1619 and 1791), January 2001.), the investigators examined whether the low levels of mercury derived from amalgam were associated with subtle neuropsychological deficits in a population of healthy, employed adults (age 30-49). This cross-sectional epidemiological study recruited 550 men and women for a study of dental health and general well being. Data from a modified oral examination, laboratory assays, structured questionnaire, and neuropsychological test battery were used in this analysis. The authors concluded that no statistically significant associations were found for any exposure measure or any of the outcomes. These results contradict any limited evidence that low-level mercury exposure, derived from dental restorations, is associated with neuropsychological function in healthy, employed adults in this age group.

- Pendergrass J.C., Haley B.E., Vimy M.J., Winfield S.A. and Lorscheider F.L., "Mercury vapor inhalation inhibits binding of

GTP to tubulin to rat brain: similarity to a molecular lesion in Alzheimer diseased brain." Neurotoxicology 1997;18(2):315-24.

Since it is well known that Hg vapor is continuously released from "silver" amalgam tooth fillings and absorbed into the brain, in this study rats were exposed to mercury vapor 4 hours/day for 0, 2, 7, 14 and 28 days at 250 or 300 micrograms Hg/cubic meter air, concentrations present in the mouth air of some humans with many amalgam fillings. Conclusions: The average rat brain mercury concentrations measured in this study increased significantly (11-47 fold) with duration of mercury vapor exposure. The identical neurochemical lesion of similar or greater magnitude is evident in Alzheimer brain homogenates from 80% of patients, when compared to human age-matched neurological controls. Since the rate of tubulin polymerization is dependent upon binding of GTP to tubulin dimmers, chronic inhalation of low-level mercury vapor can inhibit polymerization of brain tubulin essential for formation of microtubules.

ADA Response: The concentration of mercury vapor (250-300 ug/m³ air) used by the investigators was 5-6 times higher than the OSHA and NIOSH threshold limit values of 50 ug/m³. This is not a realistic or simulated level of mercury exposure for patients with dental amalgams.

The Pendergrass conclusions are refuted by other studies. In a series of studies published by Fung et al. (Fung Y.K., Meade A.G., Rack E.P., Blotchy A.J. et al. "Determination of blood mercury concentrations in Alzheimer's patients." J Toxicol Clin Toxicol 1995;33(3):243-7; Fung Y.K., Meade A.G., Rack E.P. et al. "Mercury determination in nursing home patients with Alzheimer's disease." Gen

Dent 1996;44(1):74-8 and Fund Y.K., Meade A.G., Rack E.P. and Blotcky A.J., "Brain mercury in neurodegenerative disorders." J Toxicol Clin Toxicol 1997;35(1):49-54.), investigators attempted to determine the concentrations of mercury in seven different brain regions from patients histologically confirmed with Alzheimer's disease, as compared to control subjects without known central nervous system and renal disorders. Brain mercury concentrations in all deceased subjects can be derived from amalgam restorations, diet, and the working environment. Based on their studies, the investigators concluded that there is no significant difference in blood and brain mercury concentrations between Alzheimer patients and aged-matched control patients, thus demonstrating that mercury derived from dental amalgam is not considered a significant factor in the pathogenesis of Alzheimer neurologic disorder.

A similar study conducted by Saxe S.R. et al. (Saxe S.R., Wekstein M.W. et al. Alzheimer's disease, dental amalgam and mercury. JADA 1999;130(2):191-9), also refutes Pendergrass. Then Saxe study consisted of 68 human subjects with diagnosed Alzheimer's disease and 33 control subjects without Alzheimer's to determine mercury levels in multiple brain regions at autopsy and to ascertain the subjects' dental amalgam status and history. The investigators concluded that mercury in dental amalgam restorations does not appear to be a neurotoxic factor in the pathogenesis of this disease. Furthermore, the authors found that brain mercury levels are not associated with dental amalgam, either from existing amalgam restorations or according to the subjects' dental amalgam

restoration histories. Moreover, dental amalgam restorations, regardless of number, occlusal surface area or time, do not relate to brain mercury level.

- Leong, CC, Syed, NI, and Lorscheider, FL., “Retrograde degeneration of neurite membrane structural integrity and formation of neurofibrillary tangles at nerve growth cones following in vitro exposure to mercury,” *NeuroReports* 2001; 12(4)233-737.

This study involved the exposure of snail neuron cells, in the culture system of the laboratory, to mercury chloride salt, which the authors claimed caused the formation of neurofibrillary tangles (NFTs) -- one of the hallmark pathological findings in the autopsy brain samples of patients who died from Alzheimer’s disease. In addition to NFTs, such abnormalities as amyloid plaques and the hyperphosphorylation of Tau protein have also been found in post-mortem brain tissues obtained from Alzheimer patients. Conclusions: These morphological changes are direct evidence that mercury is an etiological factor for Alzheimer’s disease in humans.

ADA Response: The major criticism with this paper is that the study only provides morphological data. Also, the mercury chloride concentration (20.1 ug/L) used in the study is at least five times higher than data reported by other investigators on patients with amalgam restorations. This contradicts the claim made by the authors that the mercury dose employed in the study has clinical relevance in humans. It is well documented and commonly known that manganese (Mn), lead (Pb) and cadmium (Cd) are neurotoxins. Yet, in the Leong study, these authors showed no adverse effects. Also, the purity of HgCl₂ salt, as well as other metal salts, were not known or provided in their study. Furthermore, the Leong

study lacked a cause-and-effect relationship establishing the sprouting assay of the neurite outgrowth study. A dose-response is needed to establish this relationship. This study has not been independently verified in other laboratories.

Finally, this study simply showed that the treatment of mercury chloride caused disruption of the membrane structure and reduction of linear growth rate of neuritis of cultured snail neurons. The authors' finding that mercury from amalgam restorations was linked "as a potential etiological factor for Alzheimer's disease" is not supported by this study.

4. Renal System

- Boyd ND, Benediktsson H, Vimy MJ, Hooper DE, Lorscheider FL 1992, "Mercury from dental 'silver' tooth fillings impairs sheep kidney function." Am J Physio. 1991;261(4Pt2):R1010-4.

In this study, twelve occlusal fillings were placed in each of six adult female sheep under general anesthesia, using standard dental procedures, and glass ionomer occlusal fillings (12) were inserted in two control sheep. Several days before dental surgery and at 30 and 60 days after placement of fillings, renal function was evaluated by plasma clearance of inulin and by plasma and urine electrolytes, urea, and proteins. Conclusions: When 12 fillings are placed in sheep teeth, the kidneys will concentrate amalgam mercury at levels ranging from 5 to 10 micrograms Hg renal tissue 4-20 weeks after placement. The authors concluded that sheep kidney function is impaired by the placement of dental amalgams.

ADA Response: In 1992, Boyd's study was severely criticized by Malvin et al. ("Mercury from dental 'silver' tooth fillings – letter. Am J Physiol 262

R 716-717). Malvin, a well-known renal physiologist from the University of Michigan School of Medicine, indicated that the evidence provided by Boyd et al. did not demonstrate nephrotoxicity as a result of the placement of dental amalgam. Furthermore, the data presented in the paper is incompatible with the conclusion. The only result in the paper that appears to support the conclusion is the 60% decrease in the glomerular filtration rate (GFR) of sheep that received 12 amalgam fillings. Malvin et al. questioned the validity of the GFR data. Malvin pointed out errors in the inulin clearance technique used to measure the GFR, noting that “the clearance methods are so poorly described that they are not possible to understand.”

Furthermore, critical data necessary to interpret the results are not presented. The data are not self-consistent, and the evidence for a reduced GFR was based on faulty and poorly described inulin clearance methods and were contradicted by the urea data. Also, data in the paper are inconsistent with mercury nephrotoxicity, and there was a lack of appropriate controls.

Three human studies, published later, further rejected the link between dental amalgam and renal dysfunction. First, in 1995, Herrstrom et al. published “Dental amalgam, low-dose exposure to mercury, and urinary proteins in young Swedish men” (Arch Environ Hlth 1995; 50:103-107). In this paper, the authors conclude that no significant relationship was found between any of the proteins (e.g., albumin, alpha-microglobulin, kappa and lambda light chains, and N-acetyl-beta-D-glucosaminidase) and amalgam or urinary mercury. Furthermore, the authors concluded that the study’s results did not suggest that amalgam fillings

cause kidney dysfunction in humans.

The second study was reported by Sandborgh-Englund et al. in 1996 ("No evidence of renal toxicity from amalgam fillings." *Am J Physiol* 271:R941-945). The aim of this study was to determine whether signs of renal toxicity could be observed in humans exposed to inorganic mercury from amalgam fillings in conjunctions with dental treatment. In ten patients, all amalgam restorations were removed during one single treatment session. One week before and 60 days after removal, the glomerular filtration rate (GFR) was determined by the Cr(51)-EDTA clearance techniques. No detectable effects occurred on excretion of NAG, Beta(2)-microglobulin, or albumin. The authors concluded that no signs of renal toxicity could be found in conjunction with mercury released from amalgam fillings.

One additional study was conducted at the Health Screening Program, held annually at the American Dental Association's Annual Meeting (Naleway C, Chou, FIN, Muller I, Dabney J, Roxe D, and Siddiqui F. "On-site screening for urinary Hg concentrations and correlation with glomerular and renal tubular function." *J Public Health Dentistry* 51(1),12-17, 1991). At the ADA 1985-1986 Annual Sessions, an on-site screening for mercury was conducted to identify dentists having elevated urinary mercury concentrations. The data generated from this study were used to examine the relationship between elevated urinary mercury exposure and kidney dysfunction. An analysis for the clinical markers indicated no clear relationship between elevated urinary mercury concentrations and kidney dysfunction.

5. Immune System

- Hultman P, Johansson U, Turley SJ et al. "Adverse immunological effects and autoimmunity induced by dental amalgam and alloy in mice." 1994; 8(14):1183-90.

In 1994, Hultman et al. implanted 8-100 mg silver amalgam or silver alloy, for 10 weeks or 6 months, in the peritoneal cavity of female SJL/N mice. The authors claimed that chronic hyperimmunoglobulinemia, serum IgG auto-antibodies targeting the nucleolar protein fibrilarin, and systemic immune-complex deposits developed in a time- and dose-dependent manner after implantation of the amalgam or alloy. Furthermore, splenocytes from mice implanted with amalgam or alloy allegedly showed an increased expression of class II molecules. The functional capacity of splenic T and B cells was also purportedly affected in a dose-dependent way. Conclusions: The authors hypothesize that, under appropriate conditions of genetic susceptibility and adequate body burden, heavy metal (Hg and silver) exposure from dental amalgam may contribute to immunological aberrations, which could lead to overt autoimmunity.

ADA Response: Hultman's study was later challenged by Langworth in a human study. Langworth's paper, "Minor effects of low exposure to inorganic mercury on the human immune system," was published in Scand J Work Environ Health 1993;19(6):405-13. In this study, the influence of exposure to inorganic mercury on the immune system was examined in 36 workers, who were occupationally exposed to mercury vapor, and a control group without known mercury exposure. The authors concluded that virtually all of the immunologic

parameters were within normal ranges and did not differ significantly between the two groups. Only a few individuals known to be sensitive to amalgam demonstrated minor reduction of the in vitro production of both tumor necrosis factor alpha and IL-1. No significant correlations were noted between different mercury exposure estimates and the immunologic parameters.

C. Conclusion of ADA Scientific Review

ADA believes that there is no valid or persuasive scientific evidence to suggest that those with dental amalgam restorations will experience adverse health effects except in the rare case of an allergic reaction. ADA supports ongoing research in the development of new materials that it hopes will someday prove to be as safe and effective as dental amalgam. However, the ADA continues to believe that amalgam is a valuable, viable and safe choice for dental patients and concurs with the findings of the U.S. Public Health Service that amalgam has “continuing value in maintaining oral health.” 16/

IV. The Proposed Rule Should Preempt State Laws Regarding Dental Amalgam Products

ADA submits that the proposed rule should operate to preempt state laws that conflict with the requirements encompassed by the proposed rule. State laws regarding disclosure requirements for products that contain dental mercury or calling for the abolishment of dental amalgam products are directly at odds and

16/ HHS News, January 21, 1993.

incompatible with the federal requirements set forth by FDA. Consequently, such state laws should be considered preempted by the proposed rule on dental amalgam products. It is not in the public interest to have competing state requirements that conflict with the special controls proposed by the Agency, nor is it appropriate under the FDC Act to permit states to ban the sale of dental amalgam products, which are cleared to market by FDA. In sum, as explained more fully in the following paragraphs, ADA maintains that the Agency should consider such conflicting state laws unacceptable and preempt them with the proposed rule under consideration.

A federal agency issuing an order or regulation within the scope of its delegated authority also may preempt state law, as long as the agency clearly communicates its intent to do so. See Hillsborough County, Florida v. Automated Medical Laboratories, 471 U.S. 707, 718 (1985); see also City of New York v. FCC, 486 U.S. 57, 63-64 (1988); Brookhaven Cable TV v. Kelly, 573 F.2d 765, 768 (2d Cir. 1978). Congress, through the Medical Device Amendments of 1976 (“MDA”) to the FDC Act, clearly communicated its intent to allow FDA to preempt state laws that conflict with federal requirements for medical devices.

The MDA contains an express preemption provision regarding FDA’s regulation of medical devices. Section 521 provides for preemption of state requirements applicable to a medical device that are “different from, or in addition to, any requirement applicable under this chapter to the device, . . . and which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.” FDC Act § 521.

FDA has promulgated a regulation interpreting section 521, which states:

State . . . requirements are preempted only when . . . there are . . . specific [federal] requirements applicable to a particular device . . . thereby making any existing divergent State . . . requirements applicable to the device different from, or in addition to, the specific [federal] requirements. 17/

21 C.F.R. § 808.1(d). Furthermore, the Supreme Court has interpreted FDA's preemption regulation to mean that:

[I]n most cases a state law will be pre-empted only to the extent that FDA has promulgated a relevant federal "requirement." Because the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the [FDC] Act, the agency is uniquely qualified to determine whether a particular form of state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress."

Medtronic v. Lohr, 116 S.Ct. 2240, 2255 (1996). The Court found that when Congress enacted section 521, it "was primarily concerned with the problem of specific, conflicting State statutes and regulations rather than the general duties enforced by common-law actions." Id. at 2252. The Court understood the "overarching concern" of section 521 to be "that pre-emption occur only where a

17/ It is acknowledged that FDA's regulation provides that section 521 does *not* preempt state requirements that: (1) are generally applicable to products other than devices; (2) are equal to, or substantially identical to, federal requirements; (3) impose occupational licensure (*e.g.*, physicians, device distributors); or (4) involve general enforcement for all devices (*e.g.*, state registration and licensing of device manufacturers). 21 C.F.R. § 808.1(d)(1), (2), (3) & 6(i). The state laws regarding dental amalgam products do not fall within these four categories of exemptions.

particular state requirement threatens to interfere with a specific federal interest.”
Id. at 2257.

Federal courts have applied the principles set forth in Medtronic to deny claims based on state laws that conflict with FDA’s regulations, concluding that the federal regulations preempt the contrasting state law. For example, in Martin v. Teletronics Pacing Systems, Inc., 105 F.3d 1090 (6th Cir. 1997), the plaintiff brought an inadequate warning claim under state law for an approved investigational pacemaker. The plaintiff claimed that the warnings for the pacemaker, which was subject to an investigational device exemption (“IDE”) under the FDC Act, did not comply with state laws requiring more detailed warnings as compared to those under the FDC Act. In denying the claim because the state law was preempted by the federal regulations regarding warnings for IDE medical devices, the Court stated “the state requirement would impede the implementation and enforcement of specific federal requirements. To allow a state cause of action for inadequate warnings would impose different requirements or requirements in addition to those required by federal regulations.” Id. at 1100.

The Martin Court similarly rejected plaintiff’s state law products liability claims by way of preemption. The plaintiff asserted manufacturing and design defect claims based on state law that, again, conflicted with the federal requirements for manufacture and design of an investigational device. Holding that plaintiff’s state law claims were preempted, the Court reiterated that the state

products liability laws constituted “the kind of requirement that would impede the implementation and enforcement of specific federal requirements.” Id. at 1099.

Likewise, in Enlow v. St. Jude Medical, Inc., 171 F. Supp.2d 684 (W.D. Ky 2001), the Court preempted certain state strict liability laws with respect to medical devices because such laws were at odds with the MDA. The plaintiff’s claims were thus denied because there was no longer a basis on which to seek relief as a result of preemption. The plaintiff in Enlow brought design, manufacturing, and failure to warn claims regarding a PMA-approved heart valve based on state law. Much like the Court in Martin, the Enlow Court decided that conflicting state and federal regulations detailing such manufacture, design, and warning requirements for a medical device could not co-exist, stating:

Therefore, under the state requirement, the fact finder could determine the FDA approved product design renders the mechanical heart valve unreasonably dangerous. Since the state requirement differs from the federal requirement, plaintiff’s claims for defective design must be preempted. . . . To the extent plaintiff’s manufacturing defect claim alleges that St. Jude Medical’s mechanical heart valve was defective despite its adherence to the FDA approved manufacturing processes, it imposes a requirement different from the federal requirements and is accordingly preempted.

Enlow, 171 F. Supp.2d at 690. See Kemp v. Medtronic, Inc., 231 F.3d 216 (6th Cir. 2000) (holding that negligence per se, fraud, and failure to warn claims were preempted by MDA because of conflicting state and federal requirements).

These cases make clear that through the MDA, the FDC Act should preempt any state laws banning dental amalgams or requiring labeling significantly contradicting that required by FDA. Such state laws are clearly “specific,

conflicting State statutes and regulations” that “stand[s] as an obstacle” to a “relevant federal ‘requirement.’” Competing labeling standards between a state and federal requirement will lead to confusion, and an outright ban on dental amalgam products plainly conflicts with the classification scheme proposed by the Agency. Congress expressly provided for federal preemption of state laws regarding medical devices for just this type of situation, and ADA strongly believes that the proposed rule should be construed as preempting all state regulations regarding dental amalgam products which are in significant contravention of the FDA imposed federal requirements.

V. Conclusion

FDA has spent decades analyzing scientific literature on the safety of dental amalgam products. Studies, reports, and opinions from nearly every viable source on the topic have been reviewed by the Agency prior to its issuance of the proposed rule. ADA agrees with FDA that there exists no meritorious scientific evidence to indicate that the use of dental amalgam products will result in adverse health effects. The benefits of these products clearly outweigh their potential risks, and as such a uniform class II classification regulation with special controls is appropriate for encapsulated amalgam, amalgam alloy, and dental mercury. The special controls specifically address the risks associated with these products for those with allergies to the ingredients in dental amalgam and for those occupationally exposed persons who may mishandle dental amalgam products. These special controls do adequately provide a reasonable assurance of the safety

and effectiveness of the dental amalgam products. In addition, a formal evidentiary hearing on the proposed rule is not required or necessary, for such a hearing would not be in the public interest. Finally, the proposed rule should operate to preempt conflicting state laws and regulations regarding dental amalgam products.